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EXAMINER

DEVI, SARVAMANGALA J N

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25

Please find below and/or attached an Office communication concerning this application or proceeding.

[illegible]

Part of Paper No. 25

Request for Continued Examination

1) A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. 1.114. The Applicants' submission filed on 07/10/02 (paper no. 23) has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 07/10/02 (paper no. 24) in response to the final Office Action mailed 01/11/02 (paper no. 17).

Status of Claims

3) Claim 82 has been canceled via the amendment filed 07/10/02.
Claims 80, 81 and 83-93 have been amended via the amendment filed 07/10/02.
Claims 73-81 and 83-93 are pending in this application.
Claims 80, 81 and 83-93 are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

6) The objection to claim 80 made in paragraph 17(a) of the Office Action mailed 07/14/00 (paper no. 7) is withdrawn in light of Applicants' amendment to the specification.

7) The objection to claim 80 made in paragraph 17(b) of the Office Action mailed 07/14/00 (paper no. 7) is withdrawn in light of Applicants' amendment to the specification.

Specification - Informalities

8) The specification is objected to for the following reason(s):

(a) The use of trademarks in the instant specification has been noted in this application. For example, see page 21, line 9: "Elida V"; page 20, line 2: "Sephadex G-50"; page 22, line 17: "Sepharose"; page 20, line 34: "Brij 35"; and page 22, line 33: "centriprep 30". The recitations should be capitalized wherever they appear and be accompanied by the generic terminology. Each letter of the trademark must be capitalized. See M.P.E.P 608.01(V) and Appendix I. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification to make similar corrections to the trademarks, wherever such recitations appear.

(b) Lines 12-17 on page 24 of the specification are objected to for the recitations "Panel A", "Panel B", "Panel C" etc., It is suggested that Applicants replace these recitations with --Figure 4A--, --Figure 4B--, --Figure 4C-- etc.,

Rejection(s) Moot

9) The rejection of claim 82 made in paragraph 13 of the Office Action mailed 01/11/02 (paper no. 17) under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 26-33 of the U.S. Patent 5,866,135 is moot in light of Applicants' cancellation of the claim.

10) The rejection of claim 82 made in paragraph 14(h) of the Office Action mailed 01/11/02 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

11) The rejection of claim 82 made in paragraph 15 of the Office Action mailed 01/11/02 (paper no. 17) under 35 U.S.C § 112, first paragraph, as being indefinite non-enabled with regard to the scope, is moot in light of Applicants' cancellation of the claim.

12) The rejection of claim 82 made in paragraph 16 of the Office Action mailed 01/11/02 (paper no. 17) under 35 U.S.C § 112, first paragraph, as containing new matter, is moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

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- 13) The rejection of claim 80 made in paragraph 14(a) of the Office Action mailed 01/11/02 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.
- 14) The rejection of claim 80 made in paragraph 14(b) of the Office Action mailed 01/11/02 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.
- 15) The rejection of claim 80 made in paragraph 14(c) of the Office Action mailed 01/11/02 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.
- 16) The rejection of claim 90 made in paragraph 14(d) of the Office Action mailed 01/11/02 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.
- 17) The rejection of claim 93 made in paragraph 14(e) of the Office Action mailed 01/11/02 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.
- 18) The rejection of claim 93 made in paragraph 14(f) of the Office Action mailed 01/11/02 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.
- 19) The rejection of claim 80 made in paragraph 14(g) of the Office Action mailed 01/11/02 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.
- 20) The rejection of claim 81 and 83-93 made in paragraph 14(h) of the Office Action mailed 01/11/02 (paper no. 17) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

Rejection(s) Maintained

- 21) The rejection of claims 80, 81 and 83-93 made in paragraph 15 of the Office Action mailed 01/11/02 (paper no. 17) under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is maintained for reasons set forth therein.

It is noted that Applicants have deleted the recitation "sufficient to confer an average

molecular weight of the polysaccharide large enough to be protective when said polysaccharide is conjugated to protein or protein fragment". Accordingly, Applicants' arguments with regard to these deleted limitations are moot.

Applicants contend that the specification at page 11, lines 5-19 discloses the size range of the GASP vaccine polysaccharide component to elicit a protective response in individuals (i.e., mammals): "... and n is a number of repeat units sufficiently large to define a polysaccharide of sufficient average molecular weight to be immunogenic. Preferably n is from about 1 to about 50. Even more preferably, n is from about 3 to about 30 with an optimal amount of about 20 Most preferably the average molecular weight is about 10 kilodaltons. A single repeat amount of the GASP has a molecular weight of about 500 daltons." However, this part of the specification mentions an n number for GASP which is sufficiently large enough to be immunogenic, but not protective. Applicants state:

In Example 7 of the instant application, the specification discloses that a GASP conjugate vaccine (where its polysaccharide component has an average molecular weight of 10 kilodaltons, see Example 6) was able to elicit the production of antibodies specific to GASP. This experiment, in the context of the entire specification, teaches that antibodies specific to GASP are protective against GAS infection

Applicants assert that Example 1 of the specification teaches that antibodies specific to GAS polysaccharide of formula I are protective against GAS bacteria. Applicants acknowledge that Example 1 teaches the determination of antibodies specific to GAS polysaccharides in the sera from GAS-infected individuals. Applicants cite the following sentence from page 24, lines 1-5 of the specification:

Having established that human sera do contain group A carbohydrate antibodies and that the titers of these antibodies do vary in individuals, we next addressed the question of whether these antibodies would also promote opsonophagocytosis in an *in vitro* assay system.

Applicants further state that Example 1 includes bactericidal assays, relationship between anti-CHO titers and opsonophagocytosis by human sera, studies of phagocytosis by human sera in heparinized blood versus heparin free assays and absorption experiments. Applicants point to Figure 6, and lines 1-4 on page 25 of the specification and state that all sera exhibiting antibody titers "greater than 200,000 exhibited greater than 80% killing, while three out of the four sera with titers less than 200,000 did not". Applicants assert that the absorption experiments provide

evidence that the antibodies specific to GASP in the human sera contributed to the protection. Applicants point to page 27, lines 24-28 and contend that this part of the specification states that the question of whether the carbohydrate antibodies promote opsonophagocytosis of group A streptococci has been affirmatively answered and the degree of opsonization correlated well with the level of anti-carbohydrate antibodies. Applicants state that they have amended the claims to encompass a method of eliciting protective antibodies specific to GASP.

Applicants assert that Example 7 teaches that GASP vaccines elicit the production of antibodies specific to GASP in a mammal. Applicants contend that one skilled in the art reasonably follows that the specification also supports a method of eliciting antibodies specific to GASP which are protective against GAS bacteria. Applicants allege that a reasonable correlation between *in vitro* activity and *in vivo* activity for patentability is a standard different from a standard required by the Food and Drug Administration, which requires proof of efficacy. Applicants state the following on page 10 of their amendment:

The instant specification shows that antibodies specific to GASP are produced in humans that have been **infected** with GAS bacteria; antibodies specific to GASP are opsonic, bactericidal and therefore protective; and **the claimed conjugates can elicit the production of antibodies specific to GASP.** [Emphasis added].

Applicants cite case law and state that testing for the full safety is more properly left to the FDA. Applicants assert that the claimed invention does not require undue experimentation.

Applicants' arguments have been carefully considered, but are non-persuasive.

Contrary to Applicant's statement and the statement at lines 1-4 on page 25 of the specification, Figure 6 does **not** show that all sera exhibiting antibody titers "greater than 200,000 exhibited greater than 80% killing, while three out of the four sera with titers less than 200,000 did not". It should be noted that the Office did not raise any issues with regard to the safety of the vaccine.

A patent application claiming a method of eliciting a 'protective' immune response in a subject by administration of a conjugate vaccine to a mammal has to necessarily show *in vivo* protective ability of the conjugate vaccine in a mammal, **or** *in vitro* assay results that correlate with *in vivo* protective efficacy of the conjugate vaccine. Contrary to Applicants' contention, Example 1 of the specification does not teach that antibodies to the polysaccharide of "formula I"

wherein n is 3 to 50 are 'protective'. Example 1 shows that Group A streptococcal infection induced variable levels of bactericidal group A carbohydrate antibodies in humans infected with these bacteria. Example 1 shows that not all sera from group A streptococcal infected patients contain a geometric mean group A streptococcal carbohydrate antibody titer of $>200,000$. Example 1 shows that live whole cell group A streptococci, upon infection in humans, induced a geometric mean bactericidal antibody titer of $>200,000$ in some infected patients. The specification on page 17, lines 22 and 23, recognizes that such whole cell streptococci are not desirable for use as a vaccine. The antibodies in the human sera were induced by the native and non-depolymerized GASP presented to the host immune system on the surface of whole cells of streptococci. The specification in the last paragraph of page 8 states that a CHO antibody titer of $>200,000$ (i.e., antibodies induced by group A streptococcal infection) represents 80% killing in the "bacterial assay". However, the specification does not enable one skilled in the art to perform a 'bacterial assay'. The reagents to be used in this assay, steps to be used in the assay and means of determining the end point of this 'bacterial assay' are neither described, nor are known to those skilled in the art at the time of the instant invention. Moreover, this bacterial assay was performed with the sera of humans who were not immunized with the polysaccharide of formula I conjugated to a protein or a protein fragment. The immunogen recited in the instant claims is not live whole cell group A streptococcus, but a polysaccharide of formula I (wherein n is 3 to 50) conjugated to a protein or a protein fragment after modification or treatment of the polysaccharide with several chemicals.

In order for formula I polysaccharide-protein conjugate, or formula I polysaccharide-protein fragment conjugate of the instant invention to be used in a method of eliciting a GASP-specific 'protective' immune response in a mammal, the conjugate (**not** the live whole cell Group A streptococci), with or without a clinically acceptable adjuvant, has to necessarily induce 'protective' antibodies specific to group A streptococcal polysaccharide, or a geometric mean level of ELISA GASP antibodies in a mammal immunized with the conjugate (as opposed to live whole cell Group A streptococci), which antibody level is correlative of 'protection'. A review of the instant specification reveals the following. The instant specification on pages 13 and 14 describes that formula I polysaccharide is chemically modified, or treated with sodium

borohydride or its equivalent; and selectively oxidized with sodium metaperiodate or its equivalent. The activated GASP is further modified or treated with chemicals before conjugating it to a protein carrier. The process is also described as involving some amount of cross-linking. The GASP component of formula I present in the glycoconjugate is depolymerized GASP which is chemically treated, and thus is a distinct immunogen compared to the native GASP presented on the surface of whole group A streptococci (which acts as a particulate carrier) to the human immune system during infection. The state of the art reflects that the protective efficacy of streptococcal polysaccharide-protein conjugate vaccines is influenced both by molecular size of the conjugate and molecular size of the polysaccharide used in the conjugate and also on the extent of cross-linking. See the abstract of Wessels *et al. Infect. Immun.* 66: 2186-2192, 1998.

Example 7 and Table IV show that rabbits immunized with the native unconjugated GASP elicited a geometric mean base line anti-GASP ELISA titer of ≤ 100 after the first, second and third immunizations. After first immunization, a saline solution of a GASP having an assumed molecular weight of about 10 Kd (i.e., $n \approx 20$) and covalently coupled to tetanus toxoid protein induced the same base line titer of GASP antibodies (i.e., ≤ 100) in rabbits as that elicited by the uncoupled native GASP. This conjugate in saline elicited measurable GASP antibody titers by ELISA after the second and third immunizations. However, the geometric mean ELISA titer elicited was nowhere near 200,000. Even when rabbits were immunized with this GASP conjugate admixed with a clinically acceptable adjuvant, such as aluminum hydroxide or ST, the geometric mean ELISA titer elicited after three immunizations was nowhere near 200,000. Clearly, the claimed method of eliciting 'protective' antibodies specific to GASP in a mammal is not enabled by administration of a formula I GASP-protein conjugate wherein n is about 20 (let alone a formula I GASP-protein fragment conjugate), with or without a clinically acceptable adjuvant. Rabbits immunized with the formula I GASP-protein conjugate admixed in clinically unacceptable adjuvants, such as CFA and IFA, elicited a geometric mean ELISA antibody titer that exceeded 200,000 following the second and third immunizations. However, it is important to note that CFA and IFA are not acceptable in the art of vaccines for use in a human or a human child. There is neither any showing, nor is it predictable that one skilled in the art can reproducibly and successfully practice the claimed method using a formula I polysaccharide-protein conjugate

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or a formula I polysaccharide-protein conjugate wherein n is 3 to 50. Thus, Applicants' own specification provides *prima facie* evidence for lack of enablement. The rejection stands.

22) The rejection of claims 80, 81 and 83-93 made in paragraph 13 of the Office Action mailed 01/11/02 (paper no. 17) under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 26-33 of the U.S. Patent 5,866,135 is maintained for reasons set forth therein.

Applicants state that claims "61-72 were rejected under the judicially created doctrine of obviousness-type double patenting for being unpatentable" over claims 26-33 of the US patent 5,866,135. Applicants state that they agree to file a terminal disclaimer upon allowance of the instant claims.

Applicants' arguments have been carefully considered, but are not persuasive. Claims "61-72" were not stated to be rejected in the Office Action mailed 01/11/02 (paper no. 17). Instead, via paragraph 13 of the Office Action mailed 01/11/02 (paper no. 17), claims 80-93 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 26-33 of the U.S. Patent 5,866,135. The rejection stands.

Rejection(s) under 35 U.S.C. 112, Second Paragraph

23) Claims 80, 81 and 83-93 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 80 lacks antecedent basis for the recitation "said conjugates" (see line 4 and the last line of the claim), because there is no earlier recitation in the claim of "conjugates" [Emphasis added]. Since there is an earlier recitation of a "conjugate", it is suggested that Applicants replace the recitation with --said conjugate--.

(b) Claim 80 lacks antecedent basis for the recitations: "**the** polysaccharide component" (see lines 3 and 4) and "**the** protein component or protein fragment component", because there is no earlier recitation in the claim of any polysaccharide or protein or protein fragment "component" [Emphasis added]. For proper antecedence, it is suggested that Applicants insert the recitation --comprising a polysaccharide component and a protein or a protein fragment component-- after the limitation "polysaccharide-protein conjugate or

polysaccharide-protein fragment conjugate”.

(c) Claim 80 is vague and indefinite in the recitation “protein fragment”, because it is unclear what is encompassed in this limitation. It is not clear what qualifies as a ‘protein fragment’. Does a single amino acid residue of a protein qualify as a “protein fragment”?

(d) Claims 89, 90 and 93 lack antecedent basis for the recitation “according to claim 81, wherein **the** conjugates” (see line 2), because claim 81 has antecedent support for a “conjugate” [Emphasis added]. It is suggested that Applicants replace the recitation “the conjugates” with --the conjugate--.

(e) Claims 81 and 83-93, which depend directly or indirectly from one of the base claims identified above, are also rejected as being indefinite, because of the vagueness or indefiniteness identified above in the base claim(s).

Rejection(s) under 35 U.S.C. § 112, First Paragraph

24) Claims 89-91 and 93 are rejected under 35 § U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amended claims 89, 90 and 93 are directed to a method of eliciting a protective antibodies specific to group A streptococcal polysaccharide wherein “the conjugates” of claim 81, i.e., a formula I polysaccharide-protein conjugate **and** a formula I polysaccharide-protein fragment conjugate, are administered to a mammal. However, there appears to be no descriptive support in the instant specification for such a method as claimed now, wherein more than one formula I polysaccharide conjugate are administered. Therefore, the recitation of a method wherein ‘conjugates are’ administered is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P. 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in specific part(s) of the disclosure as filed, for the above-identified limitation(s), or to remove the new matter from the claims.

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Remarks

- 25) Claims 80, 82 and 83-93 stand rejected.
- 26) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1 (CM1). The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.
- 27) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

October, 2002


S. DEVI, PH.D.
PRIMARY EXAMINER